Linaclotide, Lubiprostone, Plecanatide, and Prucalopride
Criteria for Use
November 2019

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on these drugs at the PBM INTRAnet for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive linaclotide or lubiprostone

☐ For Linaclotide, Lubiprostone, and Plecanatide: Mechanical gastrointestinal obstruction, known or suspected

☐ For Prucalopride:

__ Intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, severe inflammatory conditions of the GI tract (e.g., Crohn's disease, ulcerative colitis, toxic megacolon / megarectum)

__ Untreated or unstable depression or suicidality.

__ End-stage renal disease requiring dialysis.

☐ Age less than 18 years

☐ Presence of severe or frequent diarrhea

Note: For purposes of these criteria and as causes of chronic constipation, irritable bowel syndrome (IBS) and chronic idiopathic constipation (CIC) exclude drug-induced chronic constipation and chronic constipation due to neurogenic and non-neurogenic disorders.

Inclusion Criteria

All criteria for each diagnosis must be met.

For linaclotide or plecanatide in patients with irritable bowel syndrome with constipation (IBS-C):

☐ Men or women 18 years or older with IBS-C

☐ Intolerance or inadequate response to a 1-month trial of either PEG-3350 powder for oral solution or other osmotic laxative (e.g., lactulose, sorbitol, magnesium (Mg) citrate, Mg hydroxide, glycerin rectal suppositories (RS)), unless there is a contraindication or risk factor(s) for serious adverse event(s)

GI consultation (including e-consult) is highly recommended prior to using linaclotide or plecanatide for IBS-C.

For lubiprostone in patients with irritable bowel syndrome with constipation (IBS-C)*:

☐ Women 18 years or older with IBS-C

☐ Intolerance or inadequate response to a 1-month trial of either PEG-3350 powder for oral solution (17 g twice daily) or other osmotic laxative (e.g., lactulose, sorbitol, magnesium (Mg) citrate, Mg hydroxide, glycerin rectal suppositories (RS)), unless there is a contraindication or risk factor(s) for serious adverse event(s)

GI consultation (including e-consult) is highly recommended prior to using lubiprostone for IBS-C.

For linaclotide, lubiprostone, plecanatide, or prucalopride in patients with a diagnosis of chronic idiopathic constipation (CIC):

☐ Men or women 18 years or older with CIC

☐ Intolerance or inadequate response to 1-month trials of the following agents, unless there is a contraindication or risk factor(s) for serious adverse event(s):

- □ At least one bulk forming laxative (e.g., psyllium, oxidized cellulose, calcium polycarbophil) with fluids
- □ Either PEG-3350 powder for oral solution (17 g twice daily) or other osmotic laxative (e.g., lactulose, sorbitol, magnesium (Mg) citrate, Mg hydroxide, glycerin rectal suppositories (RS))

GI consultation is highly recommended to diagnose and evaluate CIC.

For lubiprostone in patients with opioid-induced constipation (OIC):†

☐ Men or women 18 years or older with OIC

☐ Taking opioids for chronic, non-cancer pain (including chronic pain related to prior cancer or its treatment), does not require frequent opioid dose escalation AND is documented to have opioid induced constipation (OIC).

☐ Documentation of attempts to reduce constipation by change to less constipating analgesics or reduction of opioid dose OR medical justification why changes are unable to be made in current regimen.

☐ Documentation that benefits of opioid therapy exceed risks for this patient and all VA / DOD Directives / guidelines for prescribing and monitoring long-term opioids are being followed. See ***Practice Standards for Provision of Opioid Therapy*** under *Issues for Consideration*.

☐ Intolerance or inadequate response to 1-month trials of the following agents, unless there is a contraindication or risk factor(s) for serious adverse event(s):

- □ One stimulant laxative (e.g., bisacodyl, sennosides)
- □ PEG-3350 powder for oral solution (17 g twice daily) or other osmotic laxative (e.g., lactulose, sorbitol, magnesium (Mg) citrate, Mg hydroxide, glycerin rectal suppositories (RS))

Bulk forming laxatives are relatively contraindicated in OIC. A stool softener (e.g., docusate) is considered to be of low benefit and low harm for OIC and may be used but is not required prior to use of lubiprostone in OIC.

†Linaclotide, plecanatide, and prucalopride are not indicated for OIC.

Issues for Consideration

Use the more cost-effective agent for initial therapy

- *For IBS-C in women and for CIC in men or women*: Linaclotide and lubiprostone are only moderately efficacious in increasing spontaneous bowel movements and improving abdominal pain. There have been no active-comparator trials with linaclotide and lubiprostone; however, neither linaclotide nor lubiprostone seem to be superior in efficacy in indirect comparisons, and these agents have similar adverse effect profiles with minimal systemic absorption. For CIC, separate placebo-controlled trials showed that plecanatide had an NNT of 11 and linaclotide had an NNT of 6–7 in the percentage of patients with complete spontaneous bowel movements, and prucalopride had an NNT ranging from 5 to 11 for the percentage of patients achieving an average of ≥3 spontaneous complete bowel movements per week over 12 weeks. Different Rome criteria were used for diagnosis of functional constipation. There is less long-term safety data and clinical experience with plecanatide and prucalopride than linaclotide and lubiprostone.
- *For IBS-C in men*: Linaclotide or plecanatide is preferred, since lubiprostone did not show evidence of efficacy in men with IBS-C.

Lubiprostone Efficacy Is Not Established for OIC in Patients Taking Diphenylheptanes / Methadone

- Efficacy results for lubiprostone in patients with OIC who are treated with diphenylheptanes / methadone have been inconsistent.
- Diphenylheptanes / methadone may cause a dose-dependent reduction in the activation of chloride channel-2 (ClC-2) by lubiprostone in the gastrointestinal tract, thereby possibly decreasing the efficacy of lubiprostone in a dose-dependent fashion.
- Patients taking methadone who are started on lubiprostone for OIC should be re-assessed on a regular basis to determine whether treatment is effective.

Practice Standards for Provision of Opioid Therapy

- General principles, defined by CDC and VA/DoD Clinical Practice Guidelines for prescribing of opioids for chronic pain, should be utilized to guide management of long-term opioid therapy. Practitioners should obtain informed consent from each patient after explaining the risks, benefits, and obligatory terms of long term treatment with opioids. All federal and state guidelines on prescribing and dispensing opioids should be strictly followed. There should be an initial and periodic checking of the respective SPDMP (if available), consideration of provision of naloxone rescue, and exercise of other strategies to mitigate risk of chronic opioid therapy. Providers should ensure risk mitigation strategies are in place when starting opioids per the VA / DOD Clinical Practice Guideline on the Management of Opioid Therapy (OT) for Chronic Pain (2017) https://www.healthquality.va.gov/. These strategies include an informed consent conversation covering the risks and benefits of opioid therapy as well as alternative therapies. Other strategies and their frequency should be commensurate with risk factors and include: ongoing, random urine drug testing (including appropriate confirmatory testing); checking state prescription drug monitoring programs; monitoring for overdose potential and suicidality; providing overdose education; and prescribing of naloxone rescue and accompanying education.

Dyspnea Associated with Lubiprostone

- In clinical trials, 3% of patients with CIC, 1% with OIC, and < 1% with IBS-C experienced transient dyspnea within an hour of taking the first dose of lubiprostone. This symptom generally resolved within 3 hours.
- Dyspnea frequently recurred with repeat dosing of lubiprostone.
- For patients with underlying dyspnea, providers may prefer to use one of the other agents for CIC, OIC, or IBS-C rather than lubiprostone.

Last Revised: November 2019 (Added prucalopride for CIC and deleted docusate/stool softener requirement for CIC because of a lack of convincing evidence of efficacy. Downsized for Cerner.)

Revised: June 2018 (Added to Inclusion Criteria to reflect new indication labeling for OIC and to add elements of practice standards for opioid therapy. Added plecanatide for IBS-C.)

Revised: August 2017 (added plecanatide). Original: July 2017.

Contact: Francine Goodman, PharmD, BCPS, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services

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